Remarks and Arguments

Claims 1-22 are pending in this application. Claims 19 and 20 drawn to non-elected subject matter have been withdrawn. Claims 1-11, 13 and 16 have been amended to more particularly point out the invention. Support for the amendment can be found throughout the specification, e.g., page 2, line 34- page 3, line 28 and the claims as originally filed.

I. Double Patenting

Claims 1, 5-8, 11, 12, 21 and 22 stand rejected as allegedly unpatentable over claims 1-10 of U.S. Patent No. 7,256,042 in view of the bar against non-statutory obviousness-type double patenting. Applicants submit a terminal disclaimer with this response thereby obviating the rejection.

Claims 1, 5-8, 11, 12, 21 and 22 stand rejected as allegedly unpatentable over claims 1-10 of U.S. Patent No. 7,282,366 in view of the bar against non-statutory obviousness-type double patenting. Applicants submit a terminal disclaimer with this response thereby obviating the rejection.

II. 35 U.S.C. § 112 1st Paragraph

A. Enablement

Claims 1-18, 21 and 22 stand rejected as allegedly not enabled. The Office admits that the claims are enabled for no less than 5 different embodiments, but nonetheless concludes that the claims are broader than the scope of enablement provided by the specification. Applicants disagree and thus traverse the rejection.

1. The Legal Standard

As long as the specification discloses at least one method of making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. §112 is satisfied. *In re Fisher* 166 USPQ 18, 24 (CCPA 1970); *John Hopkins University v. Cellpro Inc.* 152 F3d 1342, 1361 (Fed Cir. 1998); *Amgen Inc. v. Hoechst Marion Roussel Inc.* 314 F.3d 1313, 1335 (Fed. Cir. 2003). A disclosure enables a claim if it contains sufficient information such that a skilled artisan in the pertinent art can make and use the claimed invention without undue experimentation. *In re Wands* 8 USPQ 2d 1400 (Fed. Cir. 1988). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation *In re Certain Limited-Charge Cell Culture Microcarriers* 221 USPQ 1165 (Int'l Trade Comm'n 1983). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. *Wands*, supra at 737.

2. The Specification Is Enabling

The Office admits that the specification provides an enabling disclosure for no less than 5 embodiments. But the Office seeks to limit Applicants claim scope to the particular working examples. There is no basis in the law for such a limitation. "Nothing more than objective enablement is required and therefore it is irrelevant whether the teaching is provided through broad terminology or illustrative examples. *In re Wright* 999 F.2d 1557 (Fed. Cir. 1993). Moreover given the guidance provided by the five admittedly enabled embodiments the highly skilled artisans practicing in the field of

stem cell biology could readily determine other "means for" practicing the claimed invention.

Applicants also note that the Office is attempting to limit the claims to specific concentrations of factors and reagents. Applicants believe there is no basis in the law for such a requirement. Finding an appropriate concentration of a factor or reagent in a field where the practitioners are as highly skilled as they are here would require no more than routine experimentation well within the guidelines of *In re Wands* 858 F.2d 731 (Fed. Cir. 1988).

3. A Prima Facie Case For Lack of Enablement Has Not Been Made

In rejecting the claims for alleged lack of enablement the Office relies on three references to support its position. Applicants address each reference in turn and demonstrate the respective deficiencies of each regarding the establishment of a prima facie case of lack of enablement.

The Office first cites Verfaillie et al., (2002) Hematology 369:91 alleging that this reference demonstrates the art is unpredictable. Applicants disagree. The Office quotes the following paragraph from Verfaillie:

> Many proposed applications of human ES cells are predicated on the assumption that it will be possible to obtain pure populations of differentiated cells from the ES cultures. In might be envisioned that in order to achieve this one would treat cells with inducing agents that would convert them with high efficiency to a cell type of interest. In practice that has not proven possible **with the mouse system** (emphasis added).

Applicants note the claims recite pPS cells not murine stem cells and thus Verfaillie's comments in this regard are irrelevant to the claims at issue. Moreover, Applicants note

that the literature is replete with publications highlighting the differences between murine and primate stem cells. Skilled artisans in the field of stem cell culture frequently cannot predict whether conditions suitable for one species of stem cells will be applicable to a different species. For example it is well known in the art that LIF added to a culture media may be used to maintain murine stem cells in an undifferentiated state. The same is not true for primate stem cells (See U.S. Patent Nos. 5,843,780; 6,200,806; 7,029,913). In contrast bFGF helps maintain hES cells in an undifferentiated state, while murine stem cells depend on LIF/Strat3 pathway (Amit et al. (2000) *Dev Biol.* 227:271; Matsuda et al.(1999) *EMBO J.* 18:4261). Furthermore, BMP induces differentiation in hES cells, but is involved in self renewal of murine ES cells (Xu et al. (2005) *Nat Methods* 2:185; Ying et al. (2003) *Cell* 115:281). Applicants submit that the murine system is not a good predictor regarding the behavior of primate stem cells.

Applicants further note that Verfaillie concludes her discussion of differentiating hES cells into specific phenotypes by stating: "It is now clear that pluripotent cell lines can be generated readily from human preimplantation embryos, and that a broad range of differentiated cell types can be produced in vitro from human ES cell cultures using a variety of different approaches." (page 381 2nd column) Accordingly Verfaillie does not establish the unpredictability of differentiating hES in vitro as alleged by the Office.

Next the Office cites Lavon and Benvenisty (2005) *J. Cellular Biochemistry* 96:1193 alleging Lavon states differentiation of ES cultures is heterogeneous and there is a need to define markers that are cell specific (Office Action dated 1/9/08; paragraph bridging pages 9-10). Applicants have defined markers for hepatocytes and other

claimed cell populations. In this regard Applicants note the instant claims recite numerous cell specific characteristics which are essentially markers for the claimed cell types. Claim 1 provides a list of markers for mature hepatocytes and states that the claimed cell population has at least five of the listed characteristics. They include expression of α_1-antitrypsin, expression of albumin; expression of α fetoprotein; expression of asialoglycoprotein receptor; glycogen storage; cytochrome p450 activity; glucose 6-phosphatase activity morphological features of hepatocytes.

Claim 2 recites specific markers for fetal endoderm. Claim 3 recites markers for hepatocyte precursors.

The Office next notes that Lavon warns that AFT (α fetoprotein), TTR and FOXA2 are expressed on both liver tissue and embryonic yolk sac tissue. However, TTR and FOXA2 are not included in the hepatocyte markers recited in the claims and while α fetoprotein is, the claim states that 4 other hepatocyte markers must also be present. Thus there would be no chance that the cells encompassed by the claim would include embryonic yolk sac cells. Accordingly Lavon does not establish the unpredictability of differentiating hES in vitro as alleged by the Office.

Next the Office cites Cai et al. (2007) *Hepatology* 45:1229 and alleges Cai discloses hepatocyte differentiation efficiency is low and most reports performed only limited phenotypic or functional tests on the differentiated cells. Next the Office alleges Cai discloses an alleged potential confusion between extra-embryonic endoderm and hepatic cells Applicants first note that the differentiation efficiency is irrelevant for enablement purposes. To satisfy the enablement requirement Applicants only need show how to make and use their invention. There is no efficiency standard written into

the enablement requirement. Applicants next note that claim 1 recites a list of markers and functional characteristics of mature hepatocytes and the claim recites at least 5 must be present. These markers will prevent any confusion between extra-embryonic endoderm and mature hepatocytes. Nothing of record suggests that 5 markers are not sufficient to establish that the differentiated cells are indeed mature hepatocytes. The Office bears the burden in this regard. See MPEP 2164.06; In re Marzocchi 439 F.2d 220, 224 (CCPA 1971).

For all of the reasons set forth above Applicants submit the Office has not met its burden in establishing a prima facie case for lack of enablement.

III. 35 U.S.C. § 112 2nd Paragraph

Claims 1-18, 21 and 22 stand rejected as allegedly indefinite under 35 U.S.C. § 112 2nd Paragraph. The Office believes that claim 1 is unclear because the preamble of the claim recites "producing hepatocyte lineage cells," but the body of the claim recites producing "mature hepatocytes." Without acquiescing in the rejection, and for the sole purpose of expediting prosecution Applicants have amended the preamble to recite "mature hepatocytes." Applicants believe the amendment obviates the rejection.

Claims 2-4 stand rejected as allegedly indefinite under 35 U.S.C. § 112 2nd Paragraph. The Office believes that the term "most of" recited in each of the claims is unclear. Without acquiescing in the rejection, and for the sole purpose of expediting prosecution Applicants have deleted the term "most of" and amended the claims to recite "comprising." Applicants believe the amendment obviates the rejection.

Claims 5-7 stand rejected as allegedly indefinite under 35 U.S.C. § 112 2nd Paragraph. The Office believes that the claims are confusing and unclear because it is

not clear what factors are included in the claim. Without acquiescing in the rejection, and for the sole purpose of expediting prosecution Applicants have amended the claims to recite "media comprising one of the following." Applicants believe the amendment obviates the rejection.

Claims 8-10 stand rejected as allegedly indefinite under 35 U.S.C. § 112 2nd Paragraph. The Office believes that it is unclear which cells are referred to. Without acquiescing in the rejection, and for the sole purpose of expediting prosecution Applicants have amended the claims to recite "undifferentiated cells." Applicants believe the amendment obviates the rejection.

Claims 11, 13, and 16 stand rejected as allegedly indefinite under 35 U.S.C. § 112 2nd Paragraph. The Office believes that the claims are incomplete because the method steps do not relate back to producing hepatocyte lineage cells. Without acquiescing in the rejection, and for the sole purpose of expediting prosecution Applicants have amended the claims to recite "thereby differentiating human embryonic stem (hES) cells into hepatocyte lineage cells." Applicants believe the amendment obviates the rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this filing and charge any additional required fees to our deposit account No. 07-1139, referencing the docket number indicated above.

Respectfully submitted,

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June 9, 2008

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